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The Interaction of Sex, Height, and QRS duration on the Effects of Cardiac Resynchronization Therapy on Morbidity and Mortality: An Individual-Patient Data Meta-analysis

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Short Title: Women and CRT Clinical Response

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Abstract (Word Count: 225)

Aims: To explore possible associations that may explain the greater benefit from Cardiac Resynchronization Therapy (CRT) reported amongst women.

Methods and Results: In an individual patient data (IPD) meta-analysis of five randomized controlled trials, all-cause mortality and the composite of all-cause mortality or first hospitalisation for heart failure (HF) were compared among 794 women and 2702 men assigned to CRT or a control group. Multivariable analyses were performed to assess the impact of sex, QRS duration, HF aetiology, left ventricular end-diastolic diameter (LVEDD), and height on outcome. Women were shorter, had smaller LVEDD, more often left bundle branch block (LBBB), and less often ischaemic heart disease (IHD), but QRS duration was similar between sexes. Women tended to obtain greater benefit from CRT but sex was not an independent predictor of either outcome. For all-cause mortality, QRS duration was the only independent predictor of CRT benefit. For the composite outcome, height and QRS duration, but not sex, were independent predictors of CRT benefit. Further analysis suggested increasing benefit with increasing QRS duration amongst shorter patients, of whom a great proportion were women.

Conclusions: In this IPD meta-analysis CRT benefit was greater in shorter patients, which may explain reports of enhanced CRT benefit among women. Further analyses are required to determine whether recommendations on the QRS threshold for CRT should be adjusted for height.

(ClinicalTrials.gov numbers, NCT00170300, NCT00271154, NCT00251251).

Key Words: Cardiac resynchronization therapy, heart failure, gender, height

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established therapy for symptomatic patients with heart failure (HF), a reduced left ventricular (LV) ejection fraction (EF), and electrical dyssynchrony.[1-8] Previous reports have shown that women may obtain greater benefit than men from CRT but the reason for this has not been fully clarified. Healthy women have smaller hearts[9] and a slightly shorter QRS duration[10, 11] than men and have been reported to benefit from CRT at a shorter QRS duration.[12, 13] In trials of CRT, women are also more likely to have non-ischemic cardiomyopathy and left bundle branch block (LBBB),[14] two characteristics that are associated with greater reverse LV remodeling with CRT[15] and hence potentially, with greater clinical benefit.

Individual patient-data (IPD) meta-analysis allows investigation of the interaction amongst variables which conventional meta-analysis of aggregate data does not. In a previous IPD meta-analysis, we identified QRS duration as the only independent predictor of morbidity and mortality benefit after adjusting for other variables.[16] In this IPD meta-analysis, we explored differences in the benefits of CRT for men and women and whether these appeared directly related to sex or whether sex acted as a surrogate for other features that might provide plausible alternative explanations.

Methods

Individual patient data from five substantial randomized controlled trials comparing CRT to no CRT with at least six months follow-up sponsored by Medtronic were used in this analysis. Data were pooled on 4,317 patients comparing either CRT with no active control (no device or back-up pacing); CARE-HF,[3] MIRACLE,[1] REVERSE[4, 5] or CRT-D with ICD (REVERSE,[4, 5] MIRACLE-ICD,[6] RAFT.[7] In the control arm back-up right ventricular pacing (VVI) was programmed to allow for intrinsic rhythm as much as possible and was VVI-30 in MIRACLE[1] and VVI-35 in MIRACLE- ICD[6] and REVERSE.[4, 5]

In order to create a more homogeneous population, patients in New York Heart Association (NYHA) class I (107 patients from REVERSE) and those in atrial fibrillation or with a pre-existing pacemaker (338

patients from RAFT) were excluded. The remaining patients were in sinus rhythm with NYHA III/IV (CARE HF, MIRACLE, MIRACLE ICD) or NYHA II (MIRACLE ICD, REVERSE) and on guideline-recommended HF therapy before being randomized.

The two outcomes of interest specified for this analysis were all-cause mortality and the composite of first hospitalisation for HF (HFH) or all-cause mortality. Hospitalisations were adjudicated by committees blinded to treatment allocation in each study.

Our previous univariate analyses[16] have demonstrated that the baseline variables: age, sex, NYHA class, ischaemic aetiology, QRS duration, LVEF, beta blocker use, and systolic blood pressure predicted clinical outcomes. Thus, these variables, considered the *core covariates*, were included in all models. Prior analyses also showed QRS duration to have a linear interaction with the effect of CRT for mortality, and a non-linear interaction for the composite of mortality or first HF hospitalisation.[16]

Core-laboratory values were used for electrocardiographic measurements in all studies and for echocardiographic assessment of LVEF in all studies except RAFT. Body mass index (BMI) was calculated as (weight (kg)/[height (m)]^2). Lean body mass (LBM) was calculated using the formula of LBM = 0.29569×Weight (kg) + 41.813×Height (m) – 43.2933 for women, and LBM = 0.3281×Weight (kg) + 33.929×Height (m) – 29.5336 for men.[17]

Statistics

Analyses were conducted according to the intention-to-treat principle meaning that they included those patients who failed to receive their treatment assignment.[16] Continuously distributed data are shown as both mean and standard deviation and median, inter-quartile (IQR) and full range (FR). Categorical data are shown as percentages. Because data were pooled from multiple studies which may be heterogeneous for one or more unaccounted factors affecting outcomes, shared frailty models including the *core covariates* were used for both endpoints for each gender subgroup, with random effects for each study following a gamma distribution. Consistent with the findings of prior analyses, for mortality/first HF hospitalisation, a model

with both a linear and nonlinear interaction term between QRS duration and CRT response was fit, while for mortality alone only a linear interaction term was fit. Quantitative variables (age, LVEF, QRS duration, systolic blood pressure) were treated as continuous variables in the models. QRS duration was centered by subtracting 120 ms for each QRS duration.[2] Patients in NYHA class III were enrolled in all but one study[5] and served as the default for calculating hazard rate. To assess variability of the results, 95% bootstrap confidence intervals were determined for each set of hazard ratios.

To study sex, we first tested CRT response over the range of QRS durations separately for men and women. Next, we established significant differences in baseline characteristics between men and women regarding HF aetiology, QRS morphology, left ventricular end-diastolic diameter (LVEDD), and anthropometric data such as height, BMI, and LBM. T-tests were used to compare continuous measures, while chi-square tests were used to test ordinal and qualitative characteristics. Based on differences observed between men and women, men were partitioned into terciles by height, and frailty models including the *core covariates* (excluding sex) were fit for comparison with women. Patients were also partitioned by sex and aetiology, and event rates per 100 patient years were calculated for each subgroup.

To investigate the relationship between height and the effect of CRT further, frailty models were fit for both mortality and mortality/HF hospitalisation with the *core covariate* main effects (excluding sex), main effects for CRT, normalized QRS duration and height, and the interaction effects for CRT with normalized QRS duration and normalized height. For each interaction term, the model tested a linear interaction effect for each interaction term, and a non-linear interaction effect incorporating a third-order P-spline with 4 degrees of freedom, which allows for fitting complicated curvilinear patterns. The latter interaction term was tested to determine if the hazard ratio for CRT changes over different heights and different QRS duration subgroups in a nonlinear manner. The predicted values from each model were used to determine and plot the estimated hazard ratio of CRT for QRS duration and height as continuous measures. A similar model was fit with LBM substituted for height.

A sub-analysis was performed on the patients who also had LVEDD available, to assess whether the effect of height was a surrogate for left ventricular size. The analysis added a main effect for LVEDD and an interaction effect for LVEDD with CRT to the overall model assessing height. A sub-analysis was also done involving the subset of patients in whom left ventricular end-systolic volume (LVESV) was available.

RESULTS

Following exclusion of patients for missing LVEF, QRS width, or systolic blood pressure, a total of 3,776 (97.5% of available randomized patients) were included in some or all of the analyses (**Figure 1**). Measurements of height were missing in a further 280 patients. In an additional 1,023 patients, mainly from RAFT, LVEDD was not reported (**Figure 1**). The median (IQR) follow-up was 23.5 (6.2 – 38.3) months.

Patient characteristics

The median (IQR) age of patients was 66 (58-72) years and 794 (22.7%) were women (**Table 1**). Women were less likely to have IHD. QRS duration was 160 (146-176) ms and was similar in women and men, but women were more likely to have LBBB and less likely to have right bundle branch block (RBBB). Women were shorter by an average of almost 14 cm, lighter by an average of 13 kg, had similar BMI as men, but lower LBM. Women had a smaller LVEDD ($p<0.0001$) and LVESV ($p<0.0001$) but similar LVEF compared to men. Medication was similar between the sexes except that women were more likely to be prescribed digoxin. With regard to height (**Table 2**) 886 (32.7%) men were in tercile 1: median height of 167.6 (range 165.1-169.9) cm, 935 (34.6%) were in tercile 2: median height of 175.0 (range 173.0-176.8) cm, and 881 (32.6%) in tercile 3: median height of 182.9 (range 180.1 – 185.4) cm. QRS duration and prevalence of LBBB was similar across terciles. The height of women ranged between 120.9-185.9 cm. Due to the smaller sample size, for the purpose of the event rate analysis women heights were therefore divided in two categories based on a median of 160 cm.

CRT effect by sex in relation to QRS duration

Sex did not predict the response to CRT after accounting for other covariates. An interaction between CRT and QRS duration was observed for each sex. For the composite outcome, a non-linear interaction was observed for men (p=0.034) and for women (p=0.049). For mortality alone, a linear interaction was observed for men (p=0.0059) and, with less certainty, for women (p=0.065). For both endpoints trends toward greater benefit amongst women were observed over the QRS duration range 130-170 ms (**Figure 2A/B**).

CRT effect by aetiology and sex

QRS duration was smaller among patients with IHD in both men and women. For patients with IHD, more women (81.5%) than men (71.2%) had LBBB. Overall patients with IHD had higher event rates regardless of sex or whether they were assigned to CRT (**Table 3**). The benefits of CRT on outcomes were similar for women and men with IHD, whereas for patients without IHD the observed benefit of CRT was greater among women.

CRT effect by height and sex in relation to QRS duration

The distribution of the lowest tercile of height amongst men [168 cm (165-170)] overlapped that for women [160 cm (156-166)], with approximately 94% of women having a height within the range of the lowest tercile of men. For the composite outcome, there was a linear interaction between QRS duration and the effect of CRT for each tercile of height for men (**Figure 3A**). The estimated effect of CRT on the composite outcome was greatest in the shortest tercile of men for whom benefit appeared to persist even when QRS duration was <130ms. Similar results were noted for all-cause mortality (**Figure 3B**). The estimated effect of CRT on morbidity and mortality for the shortest tercile of men was similar to that observed for women and greater than in the two taller terciles of men. Bisecting women by height showed similar estimated hazard ratios across height among women (**Table 4**). In the patients assigned to the control group the event rates were higher in shorter patients (lowest tercile of men and lower half of women by height range).

Main modelling results for outcomes and interaction with effect of CRT

Interaction between height and CRT, accounting for other covariates, was further assessed by ignoring sex and treating height as a continuous variable. Models adjusting for previously determined significant covariate main effects, as well as interaction between QRS duration and CRT, showed a linear interaction between height and CRT (p=0.013) for mortality/HF hospitalisation (**Table 5**), but not for mortality alone. Plotting the estimated hazard ratio for both height and QRS showed that the effect of CRT on the composite outcome was most pronounced amongst shorter patients with QRS between 160 and 190 ms (**Figure 4A and B**). As can be seen in Figure 4B, the greater the QRS duration and the shorter the height, the lower the estimated hazard ratio for CRT benefit. This contour plot suggests that for patients with a QRS duration of at least 150 ms, taller patients may still benefit from CRT as the estimated hazard ratio for patients with QRS = 150 ms does not reach 1.0 until height is approximately 195 cm. For some patients with a QRS of 120-149, height may mitigate the potential benefit of CRT with regard to mortality/first HF hospitalization, as for example the estimated CRT hazard ratio for patients with QRS = 135 is less than 1 if height is less than approximately 172 cm, and the estimated CRT hazard ratio for patients with QRS = 120 is less than 1 if height is less than approximately 160 cm.

When an interaction term for sex and CRT was added to the composite outcome model, the height/CRT interaction term was no longer significant, suggesting confounding between the effect of sex and height. The model for the composite outcome was repeated substituting LBM for height, but neither the main effect for LBM (p=0.61) nor the interaction with CRT, both linear (0.089) and non-linear (p=0.28), were statistically significant.

Measurements of both height and LVEDD were available for 2,473 patients. Women had smaller left ventricular dimensions than men, but LVEDD varied little across terciles of height for men (**Table 2**). LVEDD corrected for height was similar in women and men in the shortest two terciles of height, but was smaller in the tallest men. When the model for the composite outcome was expanded to include a main effect

for LVEDD and an interaction effect for LVEDD with CRT, the interaction between height and CRT remained significant. Although the main effect for LVEDD was also significant, the interaction between LVEDD and CRT was not (*Supplementary Table 1*). This suggests that height may not simply be a surrogate for LV size.

Finally, to assess the potential confounding effect of LVESV, a model for the composite outcome was fit with interaction effects for CRT with QRS duration, and CRT with LVESV, along with main effects for age, NYHA, baseline beta blocker usage, aetiology, LVEF, QRS duration, LVESV, and systolic blood pressure. While the interaction effect for QRS duration remained significant, neither the main effect for LVESV ($p=0.32$) nor the interaction between LVESV with CRT ($p=0.85$) was significant. Consequently, further analyses including both LVESV and height were not explored.

DISCUSSION

In this individual patient data meta-analysis, height and QRS duration but not sex independently predicted the ability of CRT to reduce the composite endpoint of heart failure hospitalisation and mortality. Patients of shorter stature more consistently gained benefits from CRT across the range of QRS duration 160-190 ms. CRT also appeared to provide a greater reduction in mortality amongst shorter patients, although only QRS duration was an independent predictor of benefit. Men in the shortest tercile appeared to have a prognostic benefit from CRT even when QRS duration was <130 ms. Differences in height appeared to account for why CRT conferred greater benefit for women than for men. Sex may thus act as a surrogate for height and possibly for other factors, such as QRS morphology, aetiology of ventricular dysfunction, or LV dimensions, that all may influence the response to CRT. It is unknown, however, whether the possible confounding results in sex were masking the effects of these factors or vice versa, as the modeling could not effectively assess the possible influence of sex when adjusting for height. Men significantly more often had IHD than women, with higher observed rates across all terciles, making it less likely that our results across terciles of men were explained by difference in presence of IHD. Our results suggest that although QRS duration is the

key selection criterion for CRT, stature might also be taken into account in patient selection for CRT when QRS duration lies in the range of 130-160 ms.

Historically, in clinical trials of CRT, only 20% of patients enrolled were women, making it difficult in individual studies to interpret possible differences between the sexes in their response to CRT. Conventional meta-analysis of aggregate data increases the power to detect the effect of an intervention in subgroups but unlike IPD does not permit investigation of the interaction between sex and other variables. Our prior IPD meta-analysis showed that sex was not an independent predictor of the effect of CRT on morbidity or mortality after adjusting for other variables; only QRS duration predicted benefit.[16] In this analysis, we show that this relationship between QRS duration and the benefit of CRT exists for both men and women.

Retrospective analyses of the MADIT-CRT trial of HF patients in NYHA I-II and not included in this analysis, suggested that LBBB, a subgroup that was not pre-specified, was associated with greater benefit from CRT,[13] which has had a major impact on CRT guidelines.[2,8] LBBB is more prevalent amongst women, which might explain differences in the effect of CRT between the sexes.[11-13] Others have suggested that amongst patients with LBBB, women benefit from CRT-D at shorter QRS durations than men.[18] However, in an analysis of MADIT-CRT confined to patients with LBBB, the effect of CRT-D on both morbidity and mortality was greater amongst women,[19] suggesting that female sex contributed to CRT benefit. Accordingly, differences in the prevalence of LBBB does not appear to be key to the greater benefit of CRT amongst women. Analyses of trials of CRT other than MADIT-CRT have generally not supported a greater benefit of CRT amongst patients with LBBB.[20] In an IPD meta-analysis larger than the present one and comprising all of the main trials of CRT, including from three different manufacturers and across a range of NYHA classes, older age, QRS duration >150 ms, and female sex were associated with a greater prognostic benefit from CRT; LBBB was not an independent predictor of benefit although the authors retained it in their prognostic model.[21] However, QRS duration was not analyzed as a continuous variable, which weakens its contribution in prediction models. In the current IPD meta-analysis, where QRS duration

was used as a continuous variable, LBBB was more common amongst women but it was not an independent predictor of response after accounting for QRS duration.

In CRT trials, women are also less likely to have IHD as the cause of LV dysfunction.[14] Patients with IHD in CRT trials are less likely to have LBBB and have shorter QRS durations, smaller LV volumes, and less pronounced reverse LV remodeling after CRT,[15] all of which might be expected to lead to a worse response to CRT. In our analysis, although patients with IHD had a worse outcome than those with dilated cardiomyopathy, they obtained similar relative and therefore somewhat greater absolute benefit from CRT regardless of sex.[16] This suggests that mechanisms other than reverse remodeling account for some of the therapeutic benefits of CRT[16, 19, 22] and that IHD should not be used as a selection criterion.

In a previous single center study of 212 patients with dilated cardiomyopathy and LBBB, LV reverse remodeling with CRT was greater in women than in men and occurred at smaller QRS duration.[12] This effect was not explained by differences in body surface area but by adjustment for LV mass and end-diastolic volume.[23] In our analysis, median LVEDD was smaller amongst women compared to men regardless of tercile in height. On average, healthy women have smaller hearts than men[24] but this difference is largely accounted for by differences in height.[25] Shorter patients will have relatively more LV dilatation for a given LV dimension than a tall person. In our analysis, after correction for height, women and men in the shorter two terciles had similar LVEDD, but men in the tallest tercile had relatively less LV dilatation. The greater benefit of CRT in women and shorter men might be because of greater LV dilatation relative to their pre-morbid state. However, we did not find that LVEDD predicted benefit from CRT, whether or not height was included in the model.

Shorter patients may be at higher risk for cardiovascular events. In population studies, shorter patients are at higher risk of coronary artery disease and stroke[26] and greater risk of new onset HF.[27] In our analysis, women and men had similar BMI but, as expected,[28] LBM was lower in women as a percentage of body weight. Higher BMI is associated with a lower mortality for patients with heart failure,[25, 29] but BMI

does not distinguish between fat and lean body mass. Individuals with similar BMI may have very different body compositions.

An important limitation of this analysis was the restriction to those studies in which we had access to IPD. One distinction is that the mean age in this IPD is lower than the mean age of the overall broad HFpopulation and in HF surveys. Therefore, care should be taken in interpreting post-hoc analyses of subgroup data and in extrapolating data gathered from patients selected for a clinical trial to the wider patient population that might be considered for CRT. Therefore, and despite stemming from an individual patient data meta-analysis, our study results do not allow firm conclusions, but remain hypothesis generating. Our analysis included a large number of patients with heterogeneity in symptom severity and intervention (ICD vs. CRT) but found that no measured patient characteristic other than QRS duration and height influenced the clinical benefit of CRT. Choice of baseline covariates to evaluate was predetermined by constituent trials and predefined for this analysis. No minimum sample size was required for subgroups. Finally, many patients had missing data on ventricular dimensions and volumes which will have weakened the power to show interactions for these variables. Race was not taken into consideration in this analysis but most patients were of Caucasian origin. Whether race influences the relationship between QRS duration and the effect of CRT is unknown but amongst healthy individuals, Africans and Asians of both sexes have a shorter QRS duration than Caucasians.[10, 30]

In conclusion, QRS duration is the strongest predictor of the likelihood that CRT will reduce morbidity and mortality for patients with symptomatic heart failure, a reduced LVEF and in sinus rhythm, but patients who are shorter in height may also be more likely to benefit. Differences in height might account for the observation that women tend to benefit more from CRT than men. Whether height-corrected QRS duration should be used to select patients for CRT deserves further exploration.

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LEGENDS

Figure 1: CONSORT flow diagram showing reasons for excluding patients from analysis.

Figure 2: Estimated hazard ratios (Y-axis) and 95% confidence intervals (dotted lines) for the effects of CRT versus control for men (black lines) and women (red lines). **Panel 2A** shows the relationship between the effect of CRT on mortality or first HF hospitalisation and QRS. **Panel 2B** shows the corresponding relationship for mortality. The intersection of the 95% confidence interval and the line indicating a hazard ratio of 1.0 (no effect) indicates the QRS duration above which there is a high certainty of response.

Figure 3: Estimated hazard ratios (Y-axis) for the effects of CRT versus control with QRS, for mortality or first HF hospitalisation (**Panel 3A**) and mortality alone (**Panel 3B**) on men partitioned by height (upper tercile, middle tercile, lower tercile) and women (red lines).

Figure 4: Estimated hazard ratios (Z-axis) for the effects of CRT versus control on mortality/first HF hospitalization with QRS plotted on the X-axis and Height in cm plotted on the Y-axis. Hazard ratio 1 marked with line. (**Panel 4A)** and a Contour Plot for CRT Hazard Ratio of Mortality/First HF Hospitalization by QRS and Height (**Panel 4B).** The contours reflect the CRT hazard ratio for different combinations of QRS duration and height generated from Figure 4 a. This "overhead view" was created to facilitate the ranges of height (Y-axis) and QRS duration (X-axis) for different CRT hazard ratios. Lighter blue colour corresponds to greater CRT benefit (i.e. lower hazard ratio).

Table 1. Patient Characteristics

	Women (N=794)	Men (N=2702)	Statistical Difference Men vs Women (N=3496)
Study			
MIRACLE	154 (19.4%)	325 (12.0%)	P < 0.0001
MIRACLE ICD	103 (13.0%)	446 (16.5%)	
CARE-HF	190 (23.9%)	526 (19.5%)	
REVERSE	112 (14.1%)	390 (14.4%)	
RAFT	235 (29.6%)	1015 (37.6%)	
Age			
Mean ± STD	64.3 ± 10.8	64.9 ± 10.2	0.5 ± 10.3
Median (IQR)	65.9 (57.6 – 72.5)	66.0 (58.0 – 72.4)	P = 0.2161
Range	23.0 – 89.0	20.4 – 93.8	
QRS Duration (ms)			
Mean ± STD	161.8 ± 20.4	160.7 ± 23.3	-1.1 ± 22.6
Median (IQR)	160 (150 – 175)	160 (143 – 177)	P = 0.1854
Range	94 – 263	80 – 250	
Height (cm)			
Mean ± STD	161 ± 8	174.6 ± 7.7	13.9 ± 7.7
Median (IQR)	160 (156 – 166)	175.0 (169.9 – 180.1)	P < 0.0001
Range	121 – 186	132.1 – 200.7	
Weight (kg)*			
Mean ± STD	71.9 ± 17.0	85.1 ± 17.4	13.2 ± 17.3
Median (IQR)	69.0 (60 – 81.2)	82.8 (73.0 – 94.8)	P < 0.0001
Range	37.2 – 142.7	31.3 – 188.2	
BMI			
Mean ± STD	27.8 ± 6.5	27.9 ± 5.3	0.1 ± 5.6
Median (IQR)	26.6 (23.4 – 31.3)	27.3 (24.4 – 30.7)	P = 0.8282
Range	14.2 – 64.3	11.4 – 70.6	
Lean Body Mass (kg)			
Mean ± STD	45.2 ± 6.6	57.6 ± 7.2	12.4 ± 7.0
Median (IQR)	44.8 (40.5 – 49.1)	57.0 (52.8 – 61.8)	P < 0.0001
Range	26.5 – 69.5	35.9 – 94.3	
Ischaemic aetiology	277 (34.9%)	1719 (63.6%)	P < 0.0001
Hypertension**	363 (45.9%)	1210 (44.9%)	P = 0.6275
NYHA			
Class II	315 (39.7%)	1410 (52.2%)	P < 0.0001
Class III	433 (54.5%)	1210 (44.8%)	
Class IV	46 (5.8%)	82 (3.0%)	
Baseline MLwHF			
Mean ± STD	48.0 ± 24.0	41.4 ± 23.4	-6.6 ± 23.6
Median (IQR)	48 (28 – 67)	40 (22 – 59)	P < 0.0001
Range	0 – 105	0 – 105	
LBBB***	704 (89.0%)	2034 (75.7%)	P < 0.0001
RBBB***	29 (3.7%)	282 (10.5%)	P < 0.0001
LVEF (%)			
Mean ± STD	24.4 ± 6.2	24.1 ± 6.3	-0.4 ± 6.3

Median (IQR)	24.2 (20.0 – 28.3)	24.2 (20.0 – 28.0)	P = 0.1554
Range	8.0 – 53.4	6.0 – 51.6	
LVEDD**			
Mean ± STD	6.6 ± 0.9	7.0 ± 0.9	0.4 ± 0.9
Median (IQR)	6.5 (6.0 – 7.2)	7.0 (6.3 – 7.5)	P < 0.0001
Range	4.1 – 9.6	3.9 – 12.0	
LVESV***			
Mean ± STD	198.3 ± 85.4	241.7 ± 98.6	43.3 ± 95.4
Median (IQR)	180.8 (137.9 – 241.1)	223.9 (174.8 – 288.4)	P < 0.0001
Range	47.6 – 555.7	65.7 - 862	
Baseline Medications			
Beta Blocker	617 (77.7%)	2112 (78.2%)	P = 0.7846
ACE/ARB******	755 (95.3%)	2567 (95.2%)	P = 0.8954
Digoxin******	372 (47.0%)	1159 (43.0%)	P = 0.0472
Diuretics******	713 (90.0%)	2358 (87.5%)	P = 0.0507
Spironolactone*******	355 (47.0%)	1099 (43.7%)	P = 0.1099

*57 Subjects with missing data
**11 Subjects with missing data
***17 Subjects with missing data
****1023 subjects with missing data
*****1417 Subjects with missing data
******8 Subjects with missing data
*******223 Subjects with missing data

ACE=angiotensin converting enzyme inhibitor, AII= angiotensin II receptor inhibitor, BMI= body mass index, IQR= interquartile range, LVEF= left ventricular ejection fraction, LBBB= left bundle branch block, LVEDD= left ventricular end-diastolic diameter, LVESV= left ventricular end-systolic volume, MLwHF= Minnesota Living with Heart Failure Questionnaire, NYHA New York Heart Association class, RBBB= right bundle branch block, STD= standard deviation

Table 2: Patient Characteristics by Height Tercile for Men

	Women (N=794)	Men (Tercile 1) (N=886)	Men (Tercile 2) (N=935)	Men (Tercile 3) (N=881)
Study				
MIRACLE	154 (19.4%)	92 (10.4%)	110 (11.8%)	123 (14.0%)
MIRACLE ICD	103 (13.0%)	95 (10.7%)	158 (16.9%)	193 (21.9%)
CARE-HF	190 (23.9%)	221 (24.9%)	170 (18.2%)	135 (15.3%)
REVERSE	112 (14.1%)	101 (11.4%)	138 (14.8%)	151 (17.1%)
RAFT	235 (29.6%)	377 (42.6%)	359 (38.4%)	279 (31.7%)
Age				
Mean ± STD	64.3 ± 10.8	66.3 ± 9.6	64.7 ± 10.5	63.6 ± 10.3
Median (IQR)	65.9 (57.6 – 72.5)	67.7 (59.6 – 73.3)	65.7 (57.7 – 72.8)	64.6 (57.1 – 71.1)
Range	23.0 – 89.0	32.6 – 87.5	20.4 – 87.8	25.5 – 93.8
QRS Duration (ms)				
Mean ± STD	161.8 ± 20.4	160.5 ± 22.8	159.6 ± 23.1	162.1 ± 23.8
Median (IQR)	160 (150 – 175)	160 (144 – 176)	160.0 (140.0 – 175.0)	160 (144 – 180)
Range	94 – 263	93 - 228	80 - 240	96 – 250
Height (cm)				
Mean ± STD	161 ± 8	166.3 ± 4.6	174.8 ± 2.0	182.9 ± 4.0
Median (IQR)	160 (156 – 166)	167.6 (165.1 – 169.9)	175.0 (173.0 – 176.8)	182.9 (180.1 – 185.4)
Range	121 – 186	132.1 – 171.5	172.0 – 177.8	178.1 – 200.7
Weight (kg)*				
Mean ± STD	71.9 ± 17.0	76.9 ± 14.3	85.8 ± 16.2	92.6 ± 17.9
Median (IQR)	69.0 (60 – 81.2)	75.1 (68.0 – 85.0)	83.9 (75.2 – 94.4)	90.7 (80.5 – 102.1)
Range	37.2 – 142.7	31.3 – 186.4	34.1 – 161.9	37.2 – 188.2

BMI				
Mean ± STD	27.8 ± 6.5	27.8 ± 5.3	28.1 ± 5.2	27.7 ± 5.2
Median (IQR)	26.6 (23.4 – 31.3)	27.4 (24.4 – 30.6)	27.4 (24.7 – 30.7)	27.1 (24.1 – 30.5)
Range	14.2 – 64.3	11.8 – 70.6	11.4 – 51.2	11.5 – 56.3
Lean Body Mass (kg)				
Mean ± STD	45.2 ± 6.6	52.1 ± 5.1	57.9 ± 5.5	62.9 ± 6.4
Median (IQR)	44.8 (40.5 – 49.1)	51.8 (49.0 – 55.1)	57.3 (54.4 – 60.9)	62.1 (58.5 – 66.4)
Range	26.5 – 69.5	35.9 – 86.8	40.0 – 83.9	43.8 – 94.3
Ischaemic	277 (34.9%)	580 (65.5%)	617 (66.0%)	522 (59.3%)
Hypertension**	363 (45.9%)	392 (44.3%)	419 (45.1%)	399 (45.3%)
NYHA				
Class II	315 (39.7%)	442 (49.9%)	500 (53.5%)	468 (53.1%)
Class III	433 (54.5%)	409 (46.2%)	408 (43.6%)	393 (44.6%)
Class IV	46 (5.8%)	35 (4.0%)	27 (2.9%)	20 (2.3%)
Baseline MLwHF				
Mean ± STD	48.0 ± 24.0	40.3 ± 23.3	40.9 ± 23.5	41.6 ± 23.6
Median (IQR)	48 (28 – 67)	38.5 (21 – 57)	40 (21 – 59)	40 (22 – 59)
Range	0 – 105	0 - 105	0 - 101	0 – 100
LBBB***	704 (89.0%)	679 (77.0%)	686 (73.8%)	669 (76.4%)
RBBB***	29 (3.7%)	89 (10.1%)	103 (11.1%)	90 (10.3%)
LVEF (%)				
Mean ± STD	24.4 ± 6.2	24.1 ± 6.5	24.2 ± 6.1	23.9 ± 6.4
Median (IQR)	24.2 (20.0 – 28.3)	24.4 (20.0 – 28.0)	24.5 (20.0 – 28.0)	24.0 (19.8 – 28.0)
Range	8.0 – 53.4	7.0 – 51.6	8.9 – 48.3	6.0 – 46.8
LVEDD****				

Mean ± STD	6.6 ± 0.9	6.9 ± 0.9	7.0 ± 0.9	7.1 ± 0.9
Median (IQR)	6.5 (6.0 – 7.2)	6.8 (6.2 – 7.4)	7.0 (6.4 – 7.5)	7.0 (6.5 – 7.7)
Range	4.1 – 9.6	4.9 – 9.9	4.8 – 12.0	3.9 – 10.5
LVESV***				
Mean ± STD	198.3 ± 85.4	224.9 ± 90.3	237.5 ± 93.4	260.4 ± 107.0
Median (IQR)	180.8 (137.9 – 241.1)	207.7 (164.5 – 267.8)	220.9 (175.2 – 282.4)	237.8 (183.1 – 307.7)
Range	47.6 – 555.7	65.7 – 759.2	75.0 – 826.1	82.1 – 862.0
Baseline Medications				
Beta Blocker	617 (77.7%)	679 (76.6%)	740 (79.1%)	693 (78.7%)
ACE/ARB******	755 (95.3%)	841 (95.0%)	887 (95.4%)	839 (95.2%)
Digoxin******	372 (47.0%)	342 (38.6%)	396 (42.6%)	421 (47.8%)
Diuretics******	713 (90.0%)	780 (88.1%)	815 (87.6%)	763 (86.6%)
Spironolactone*******	355 (47.0%)	356 (45.6%)	389 (44.6%)	354 (42.8%)

*57 Subjects with missing data
**11 Subjects with missing data
***17 Subjects with missing data
****1023 subjects with missing data
*****1417 Subjects with missing data
******8 Subjects with missing data
*******223 Subjects with missing data

ACE=angiotensin converting enzyme inhibitor, AII= angiotensin II receptor inhibitor, BMI= body mass index, IQR= interquartile range, LVEF= left ventricular ejection fraction, LBBB= left bundle branch block, LVEDD= left ventricular end-diastolic diameter, LVESV= left ventricular end-systolic volume, MLwHF= Minnesota Living with Heart Failure Questionnaire, NYHA New York Heart Association class, RBBB= right bundle branch block, STD= standard deviation

Table 3. Estimated Event Rates by Sex, Aetiology, and Randomization Arm

Sex	Ischaemic	CRT (N=1970)	Control (N=1809)	QRS Duration Median (25th – 75th Percentile)	Event Rates per 100 Pt Years Mortality Rate (Mortality/HFH Rate)		Empirical Hazard Ratio: Mortality (Mortality/HFH)
					CRT	Control	
Men	Yes	1004 (65.1%)	885 (63.4%)	160 (140 – 172)	7.8 (14.4)	11.1 (21.3)	0.70 (0.68)
	No	538 (34.9%)	511 (36.6%)	164 (150 – 180)	4.5 (10.1)	7.7 (16.1)	**0.59 (0.62)**
Women	Yes	155 (36.2%)	143 (34.6%)	160 (140 – 172)	8.0 (15.0)	11.8 (24.7)	0.67 (0.61)
	No	273 (63.8%)	270 (65.4%)	160 (152 – 178)	3.3 (6.4)	7.2 (16.3)	**0.47 (0.40)**

HFH= heart failure related hospitalization

Table4. Estimated Event Rates by Sex, Tercile of Height and Randomization Arm

Gender	Subgroup by Ht: Median (IQR)	CRT Arm	Control Arm	QRS Duration Median (25^{th} – 75^{th} Percentile)	Event Rates per 100 Pt Years Mortality Rate (Mortality/HFH Rate)		Empirical Hazard Ratio: Mortality (Mortality/HFH)
					CRT	Control	
Women	Lower 50%: 156.0 (152.4 – 158.0 cm)	205	192	160 (150 – 171)	4.38 (9.34)	8.02 (20.86)	0.55 (0.48)
	Upper 50%: 166.1 (163.1 – 169.9 cm)	201	196	160 (150 – 178)	4.21 (8.66)	7.33 (15.13)	0.57 (0.57)
Men	T1: 167.6 (165.0 -169.9 cm)	460	428	160 (144 – 176)	5.59 (10.52)	10.12 (19.86)	0.55 (0.53)
	T2: 175.0 (172.9 – 176.8cm)	475	460	160 (140 – 175)	5.18 (12.91)	7.64 (17.51)	0.68 (0.74)
	T3: 182.9 (180.1 – 185.4cm)	493	389	160 (144 – 180)	5.41 (11.89)	6.86 (15.73)	0.79 (0.76)

Ht= height, HFH= heart failure related hospitalization

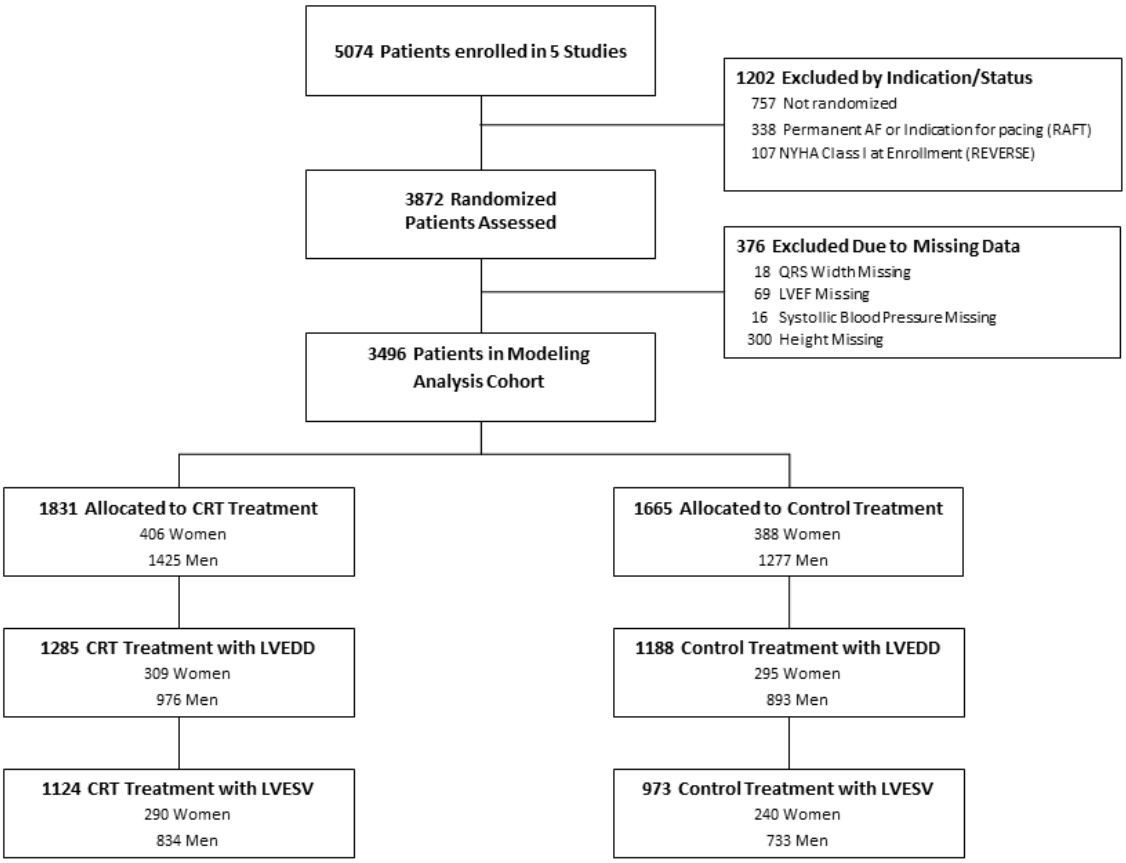
Table 5. Main Modelling Results for Time to All-Cause Mortality/HF Hospitalisation

Effect	Mortality/HF Hospitalisation		Mortality	
	Effect (Hazard Ratio)	P-value	Effect (Hazard Ratio)	P-value
Main Effects				
CRT Therapy	0.362	0.64	0.452	0.16
Age at Baseline	**1.018**	**<0.0001**	**1.039**	**<0.0001**
NYHA II	**0.640**	**<0.0001**	**0.581**	**0.0001**
NYHA IV	**1.934**	**<0.0001**	**2.213**	**<0.0001**
Ischaemic	**1.444**	**<0.0001**	**1.667**	**<0.0001**
QRS Duration	1.000	0.92	1.006	0.044
LVEF	**0.973**	**<0.0001**	**0.960**	**<0.0001**
Beta Blocker Usage at baseline	**0.818**	**0.016**	**0.786**	**0.028**
Supine Systolic BP at baseline	**0.989**	**<0.0001**	**0.987**	**<0.0001**
Height	0.992	0.096	0.999	0.92
Interaction Effects of CRT with				
QRS Duration (Linear)	**0.989**	**0.0002**	**0.986**	**0.0011**
QRS Duration (Non-linear)	**See Figure**	**0.0031**	N/A	N/A
Height (Linear)	**1.019**	**0.013**	1.018	0.083
Height (Non-linear)	See Figure	0.66	N/A	N/A
Frailty (Study to Study Differences)		**<0.0001**		**<0.0001**

Items in bold are statistically significant at p<0.05

HF= heart failure, LVEF= left ventricular ejection fraction

Figure 1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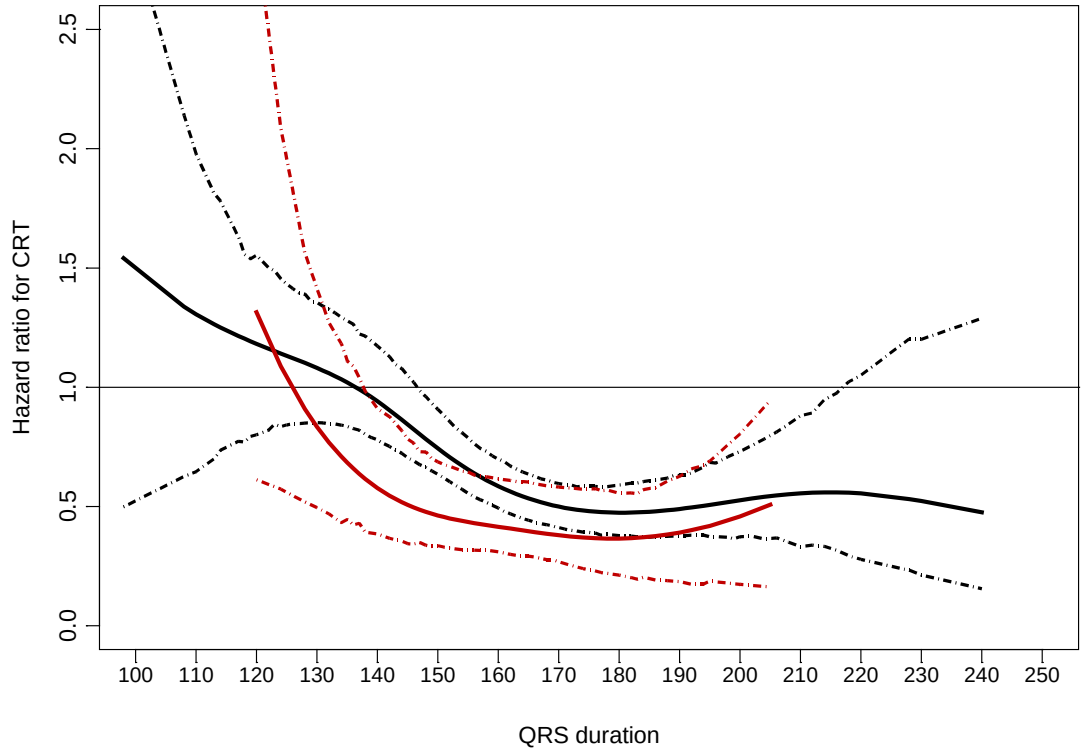
1202 Excluded by Indication/Status
757 Not randomized
338 Permanent AF or Indication for pacing (RAFT)
107 NYHA Class I at Enrollment (REVERSE)
3872 Randomized Patients Assessed
376 Excluded Due to Missing Data
18 QRS Width Missing
69 LVEF Missing
16 Systollic Blood Pressure Missing
300 Height Missing
3496 Patients in Modeling Analysis Cohort
1831 Allocated to CRT Treatment
406 Women
1425 Men
1665 Allocated to Control Treatment
388 Women
1277 Men
1285 CRT Treatment with LVEDD
309 Women
976 Men
1188 Control Treatment with LVEDD
295 Women
893 Men
1124 CRT Treatment with LVESV
290 Women
834 Men
973 Control Treatment with LVESV
240 Women
733 Men

Figure 2A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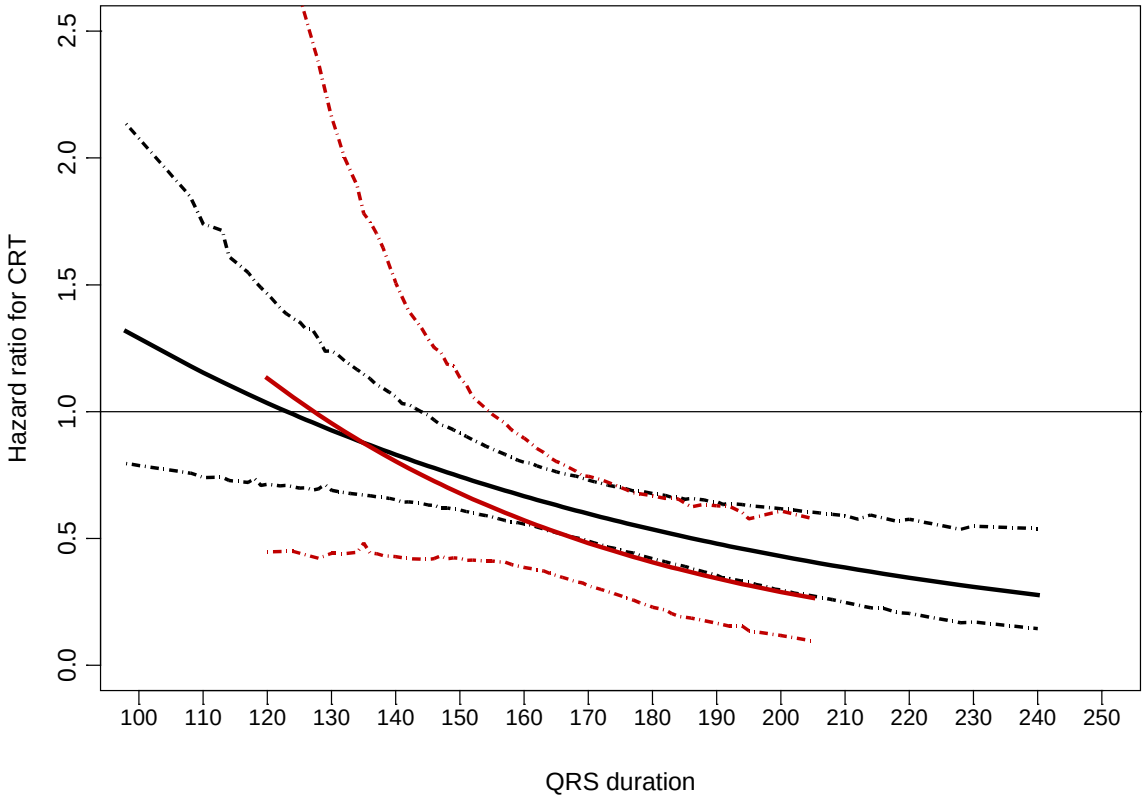
0.5
1.0
1.5
2.0
2.5
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
250
QRS duration

Figure 2B


Hazard ratio for CRT
0.0
0.5
1.0
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100
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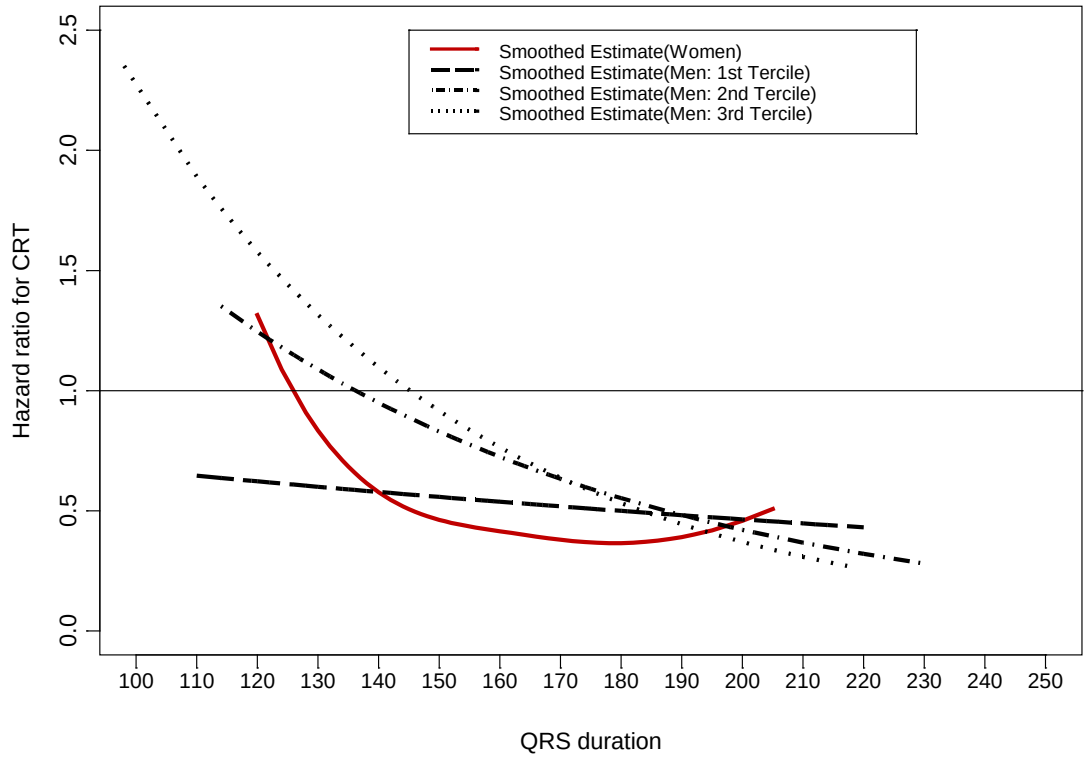
240
250
QRS duration

Figure 3A


Smoothed Estimate(Women)
Smoothed Estimate(Men: 1st Tercile)
Smoothed Estimate(Men: 2nd Tercile)
Smoothed Estimate(Men: 3rd Tercile)
Hazard ratio for CRT
0.0
0.5
1.0
1.5
2.0
2.5
100
110
120
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190
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220
230
240
250
QRS duration

Figure 3B

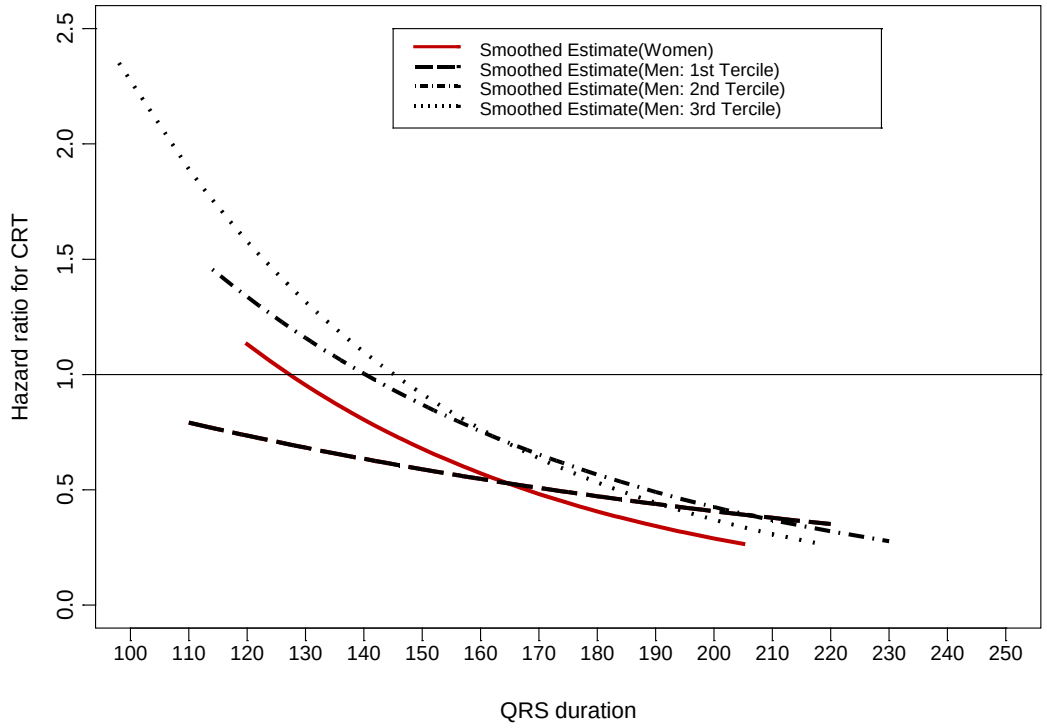

Smoothed Estimate(Women)
Smoothed Estimate(Men: 1st Tercile)
Smoothed Estimate(Men: 2nd Tercile)
Smoothed Estimate(Men: 3rd Tercile)
Hazard ratio for CRT
0.0
0.5
1.0
1.5
2.0
2.5
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
250
QRS duration

Figure 4A

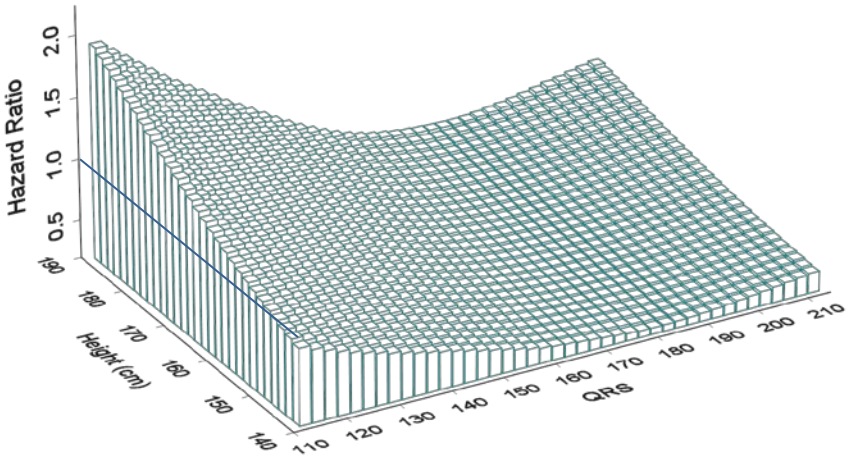
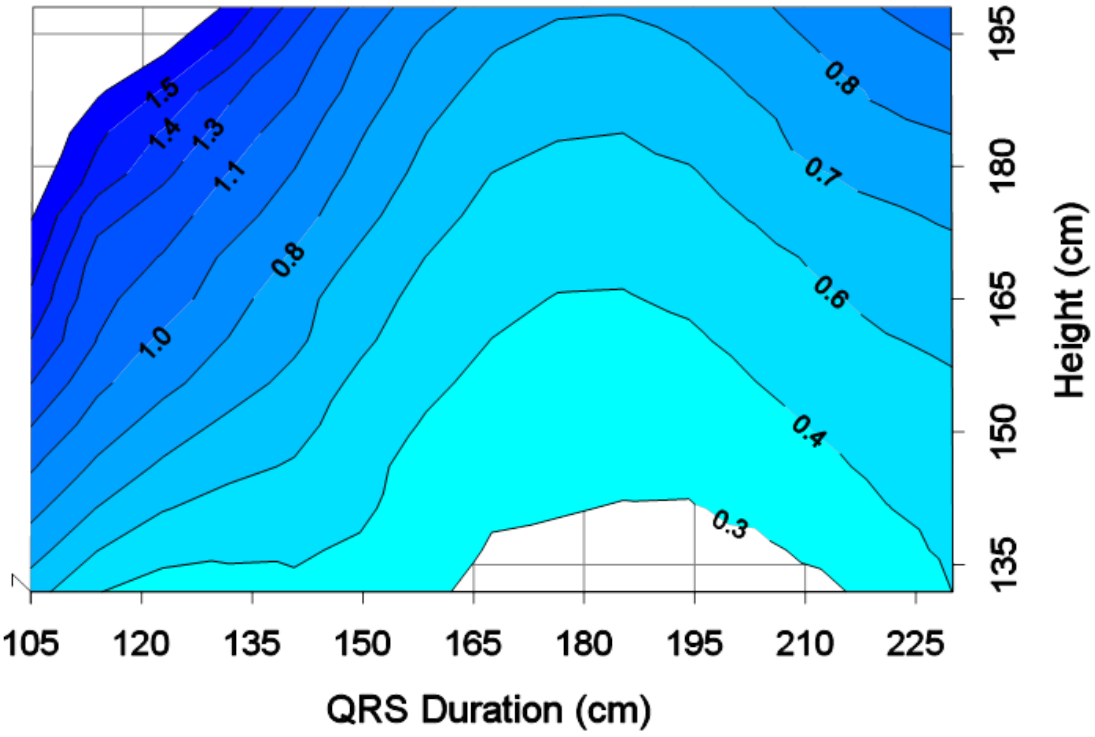

Hazard Ratio
0.5
1.0
1.5
2.0
Height (cm)
190
180
170
160
150
140
QRS
110
120
130
140
150
160
170
180
190
200
210

Figure 4B


1.5
1.4
1.3
1.1
0.8
1.0
0.8
0.7
0.6
0.4
0.3
105
120
135
150
165
180
195
210
225
QRS Duration (cm)
135
150
165
180
195
Height (cm)

Supplementary Appendix

Supplementary Table 1. Modelling Results for Time to All-Cause Mortality/HF Hospitalisation Among Subjects With LVEDD

Effect	Mortality/HF Hospitalisation	
	Effect (Hazard Ratio)	P-value
Main Effects		
CRT Therapy	0.362	0.50
Age at Baseline	**1.014**	**0.0025**
NYHA II	**0.610**	**0.0003**
NYHA IV	**1.895**	**0.0001**
Ischaemic	**1.627**	**<0.0001**
QRS Duration	0.997	0.30
LVEF	**0.974**	**0.0011**
Beta Blocker Usage at baseline	0.851	0.097
Supine Systolic BP at baseline	**0.993**	**0.0068**
Height	**1.209**	**0.0045**
LVEDD	**0.983**	**0.0034**
Interaction Effects of CRT with		
QRS Duration (Linear)	**0.991**	**0.012**
QRS Duration (Non-linear)	**Non-constant**	**0.0011**
Height (Linear)	**1.028**	**0.0029**
LVEDD (Linear)	0.918	0.36
Frailty (Study to Study Differences)		**<0.0001**

Items in bold are statistically significant at p<0.05
Only 2473 of the 3496 subjects with height available also had LVEDD and were included in this sub-analysis